end of 48 hours and continued for a variable period of time. Millikan and Eaton,[22] using larger doses than the previous authors, obtained somewhat similar results in two cases but reported no definite improvement in three other cases. As shown in Table 4, my personal experience has been limited to four patients, one of whom received cortisone and showed no evidence of improvement, with possibly some aggravation of his ophthalmoplegic manifestations.

The three patients who received corticotropin therapy showed symptomatic relapse during the course of treatment, with decided improvement starting rather abruptly about 72 hours following the termination of treatment (Fig. 2 and 3). This improvement was characterized by a considerable reduction in the neostigmine requirement and a return of strength sufficient to enable two of these patients to leave the hospital and return to ordinary activity. However, in no instance was there a complete remission, and the myasthenic manifestations remained quite evident. One of these three patients suffered a severe relapse, which developed rapidly after an interval of three months. Another course of corticotropin therapy duplicated the initial result, except that the degree of improvement was not as pronounced. Multiple remissions after repeated courses of corticotropin therapy have been reported by Torda and Wolff.[23]

SUMMARY AND CONCLUSIONS

Combined neostigmine and ephedrine medication remains the treatment of choice for most patients with myasthenia gravis. Potassium and guanidine show a relatively slight beneficial effect in comparison with neostigmine, and undesirable side effects limit their usefulness. Tetraethylpyrophosphate and octamethyl pyrophosphoramide show a maximum therapeutic effect approximating that of neostigmine but of longer duration, however, toxic reactions and difficulty in adjustment of optimum dose make their routine use impractical. Concurrence of hyperthyroidism and myasthenia gravis should be treated medically, primarily by elimination of hyperthyroidism through use of methylthiouracil or radioactive iodine, which appear to favorably influence myasthenia gravis. Thymectomy should be reserved for patients with demonstrable thymomas and a few selected patients who appear to be inadequately controlled with neostigmine and are not benefited by corticotropin (ACTH) therapy. Corticotropin therapy results in relapse during the course of therapy with noteworthy partial remission within 72 hours following termination of therapy, but subsequent relapse may occur, and ultimate therapeutic benefit remains undetermined.

ADDENDUM

Since submission of this article for publication, seven additional cases of myasthenia gravis have been treated with corticotropin. All these patients have shown a favorable response according to the characteristic "rebound" pattern, but five in the entire group have shown evidence of relapse subsequently. The degree of improvement following repetition of corticotropin therapy in most instances did not equal the initial improvement. The second patient in Table 4 received a total of four courses of corticotropin therapy and died suddenly during an acute exacerbation of myasthenia gravis on Jan. 1, 1952. This patient's illness was complicated by a refractory depressive psychosis, and he represents the only fatality in the series of patients treated with corticotropin. It would appear advisable to refrain from the use of corticotropin in those patients with myasthenia gravis who show a tendency to relapse repeatedly after a relatively short interval of improvement.

255 S. 17th St.

22. Millikan, C. H., and Eaton, L. M.: Clinical Evaluation of ACTH and Cortisone in Myasthenia Gravis, Neurology **1**: 145, 1951.

23. Torda, C., and Wolff, H. G.: The Effects of Administration of ACTH on Patients with Myasthenia Gravis, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, vol. 2, p. 126.

IMPORTANCE OF LIFE STRESS IN COURSE AND MANAGEMENT OF DIABETES MELLITUS

Lawrence E. Hinkle Jr., M.D.
and
Stewart Wolf, M.D., New York

Vagaries in the behavior of patients have long been recognized as important limiting factors in the satisfactory control of diabetes mellitus. Physicians are familiar with the fact that many adolescents omit use of their insulin, fail to sterilize their equipment, and "raid the icebox"—especially after conflicts with their parents. It is equally well known that many of the more obese patients of all ages are unable to curb their appetites and that this constitutes a major obstacle to the dietary control of a large part of the diabetic population. In addition, it has been often suspected, but not adequately demonstrated, that changes in the course of diabetes may result not only from the failure of the patient to follow the treatment regimen, but also from the direct metabolic effect of life stress. An increasing body of evidence now indicates that even when diabetic persons adhere strictly to their prescribed regimen, significant alterations in their metabolism do occur as part of their adaptation to people and events in their environment. Because of this the physician has found it necessary to concern himself more than ever with the personality of his patients and the events and situations in their lives.

From the Department of Medicine, New York Hospital-Cornell Medical Center.

Read before the Section on Internal Medicine at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, June 14, 1951.

Dr. Edward Tolstoi made available the facilities of the Diabetic Clinic of the New York Hospital for this study and criticized and encouraged this work.

THEORETICAL CONSIDERATIONS

Energy requirements in man are ordinarily fulfilled by the combustion of fat, carbohydrate, and protein in a proportion which varies according to the type and amount of food ingested and the amount of work being done. For example, during starvation a much larger proportion of fat is consumed than during periods when carbohydrate is being eaten regularly. The ability to utilize glucose is temporarily impaired; the glucose tolerance curve becomes elevated and prolonged and assumes the characteristics of a "diabetic" curve. Increasing amounts of beta-hydroxybutyric acid and aceto-acetic acid appear in the blood and urine. These "ketone bodies," once thought to be poisonous waste products of impaired fat combustion, now are recognized as valuable metabolites, readily utilized by all tissues except the central nervous system. They are normally present in human blood, but in much smaller concentration than glucose (approximately 0.2 to 2.0 mg. per 100 cc., expressed as acetone recovered), and enter readily into the Krebs cycle, the "final common path" of energy production in muscle. Accompanying these metabolic changes during early starvation there occurs a transient diuresis which is as yet unexplained.

Such changes are not confined to starvation alone. Many and varied physical stresses, such as exhausting exercise, exposure to x-rays, surgical operations, fractures of large bones, repeated vomiting, and major infections, are all known to cause ketonemia, ketonuria, and impairment of glucose tolerance in nondiabetic persons. In broad terms it may be said that any stress which leads to a diminution in the amount of carbohydrate and protein food available, or to a relatively great increase in the demands for energy, will lead to an increase in the proportion of fat burned relative to carbohydrate. The preferential utilization of fat under such circumstances appears to serve a valuable purpose. Body stores of fat are present in relatively large amount. Carbohydrate stores, on the other hand, are limited to the amount of glycogen present in the liver. When exhausted they must be replenished largely at the expense of body protein. Since a continued supply of carbohydrate is necessary for the function of the central nervous system and since the maintenance of body structure is jeopardized by the utilization of body protein, the conservation of carbohydrate and the increased utilization of fat during stress seems to be an appropriate mode of adaptation.

It is well known that physical stresses increase the insulin requirements of persons with diabetes mellitus. There has long been an impression that life situations which are stressful to the person because of their significance to him might also produce such metabolic disturbances. Cannon observed glycosuria in laboratory animals in association with fear or rage. More recently Mirsky [1] has shown that situations arousing anxiety may cause a rise in blood glucose of the diabetic, and Meyer, Bollmeier, and Alexander [2] have observed that diabetics in conflict situations may excrete an increased amount of glucose. Except for these observations, however, experimental evidence on this point has been meager.

EXPERIMENTAL STUDIES

Observations were made on a group of 64 diabetic subjects encountered in the course of routine attendance at a diabetic clinic. Ages ranged from 12 to 81, and all grades of severity of diabetes were included. With each one, by giving careful attention to his life history and personality structure, using direct and indirect methods described in detail elsewhere,[3] we made an attempt to discover his prevailing attitudes (both conscious and unconscious) and the persons and relationships important to his emotional security. Special attention was directed toward the setting in which the first symptoms of diabetes occurred, and the circumstances surrounding exacerbations and remissions. The reactions of a group of healthy nondiabetic persons to life stress were studied simultaneously in a similar fashion.[4]

In long-term studies extending over three years, periods of exacerbation and remission were correlated with events and attitudes in the life situation. Interviews with the physician were usually of an hour's duration and took place at intervals of one to three weeks. Ultimately, the patients discussed freely all aspects of their personal lives and brought to the physician their husbands, parents, and children for interviews. In essence, the physician became a family confidant, but maintained his primary affiliation with the patient. Using the technics of modern investigative psychiatry, he was able to elicit much information not usually uncovered by a brief medical history. When it appeared that a certain personal conflict was connected with the variations in the diabetic state, the pertinence of this conflict was tested in a short-term experimental setting. On the morning after an overnight fast, under carefully controlled conditions of activity, posture, and fluid intake, serial determinations of the subject's blood glucose, ketones, eosinophils, and serum inorganic phosphate and of his urinary excretion of water, chlorides, glucose, and ketones were made. Diabetic subjects were given no insulin for 24 hours before the experiments. After suitable base line observations had been made, the suspected topic of conflict was abruptly and vigorously introduced into the discussion. The interview often aroused in the diabetic patient feelings toward the interviewer similar to those he felt toward the parent, spouse, or sibling around whom the conflict centered. After an hour or more of such discussion, the interview was terminated on a reassuring and supporting note, and an effort was made to restore the original relation between the patient and the physician. However, the interview hour was not necessarily the only hour in which the subjects

1. Mirsky, I. A.: Emotional Hyperglycemia, Proc. Central Soc. Clin. Research **19**: 74, 1946.

2. Meyer, A.; Bollmeier, L. N., and Alexander, F.: Correlation Between Emotions and Carbohydrate Metabolism in 2 Cases of Diabetes Mellitus, Psychosom. Med. **7**: 335, 1945.

3. (*a*) Hinkle, L. E., Jr.; Evans, F. M., and Wolf, S.: Studies in Diabetes Mellitus: III. Life History of 3 Persons with Labile Diabetes, and Relation of Significant Experiences in Their Lives to the Onset and Course of the Disease, Psychosom. Med. **13**: 160, 1951. (*b*) Hinkle, L. E., Jr.; Evans, F. M., and Wolf, S.: Studies in Diabetes Mellitus: IV. Life History of 3 Persons with Relatively Mild, Stable Diabetes, and Relation of Significant Experiences in Their Lives to the Onset and Course of the Disease, ibid. **13**: 184, 1951. (*c*) Hinkle, L. E., Jr., and Wolf, S.: Studies in Diabetes Mellitus: Changes in Glucose, Ketone and Water Metabolism During Stress, A. Res. Nerv. & Ment. Dis., Proc. **29**: 338, 1950.

4. (*a*) Hinkle, L. E., Jr.; Edwards, C. J., and Wolf, S.: The Occurrence of Diuresis in Humans in Stressful Situations, and Its Possible Relation to the Diuresis of Early Starvation, J. Clin. Invest. **30**: 809, 1951. (*b*) Hinkle, L. E., Jr.; Conger, G. B., and Wolf, S.: Studies on Diabetes Mellitus: The Relation of Stressful Life Situations to the Concentration of Ketone Bodies in the Blood of Diabetic and Non-Diabetic Humans, ibid. **29**: 754, 1950.

were under stress. Because laboratory procedures such as these may in themselves have threatening implications for some people, because subjects may themselves introduce a stressful stimulus into an intended control procedure through their own ruminations, and because attitudes and feelings once aroused cannot always be

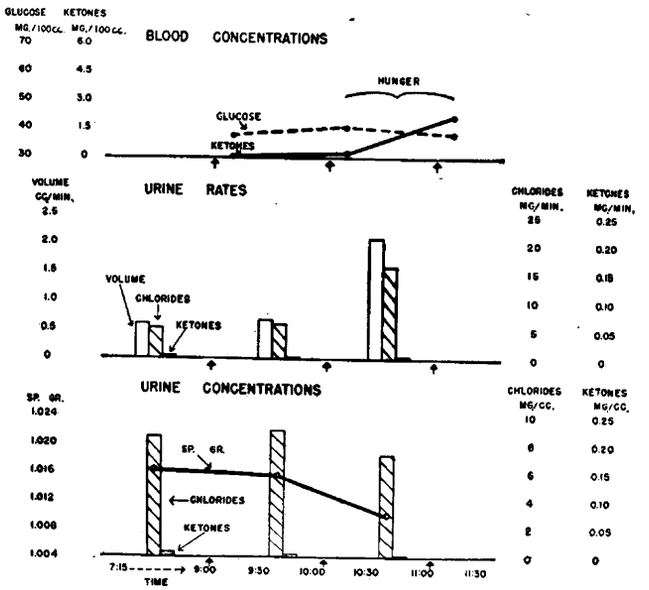

Fig. 1.—Rise in blood ketone concentration and diuresis occurring in a nondiabetic woman, 25, after 16 hours of fasting.

completely allayed in a brief period, some subjects were under stress during one or both of the hours other than the interview hours, as will be noted. The reactions of the subject to this procedure were evaluated not only by observing him carefully at the time, but also by a

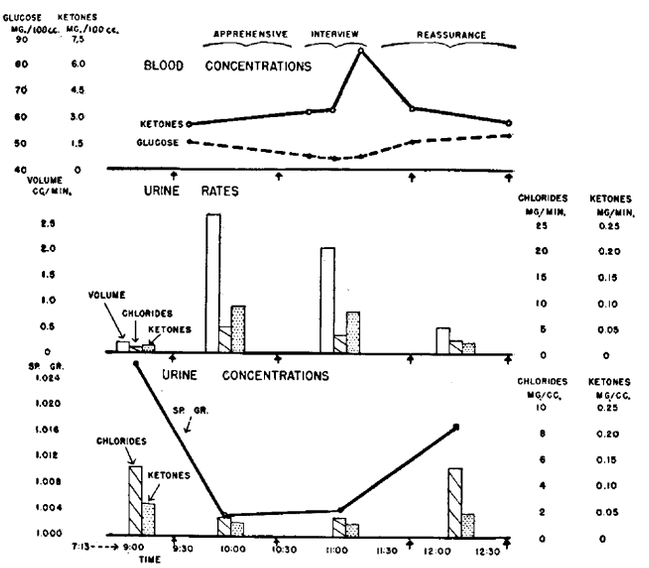

Fig. 2.—Fall in blood glucose, rise in blood ketones, and diuresis occurring in a nondiabetic woman, 42, during a stressful situation which aroused apprehension and anger.

review of his recollections and associations about the whole procedure.[5] At a later date a similar study was carried out, with the interview centering around topics known to be more neutral or reassuring to the subject. In this manner more than 200 studies have been made on over 80 persons during a three-year period.

During quiet resting the blood ketone and glucose concentrations and the rate of output of urine of nondiabetic subjects changed very little during a morning in which no food was eaten. However, with continued fasting, the glucose concentration slowly fell toward a level of about 40 to 50 mg. per 100 cc.,[6] and the blood ketone concentration rose. At about the same time there often occurred a moderate diuresis as a part of the adaptive process. This reaction observed in the fasting nondiabetic human being is shown graphically in Figure 1.

A similar phenomenon produced by a stressful situation without starvation is shown in Figure 2. A nondiabetic woman, 42, became apprehensive during the first hour while she was "waiting quietly" for what to her was an unfamiliar and threatening laboratory procedure. During the hour of interview she remained apprehensive, and, in addition, she was made angry and sad by the manner in which the interviewer discussed

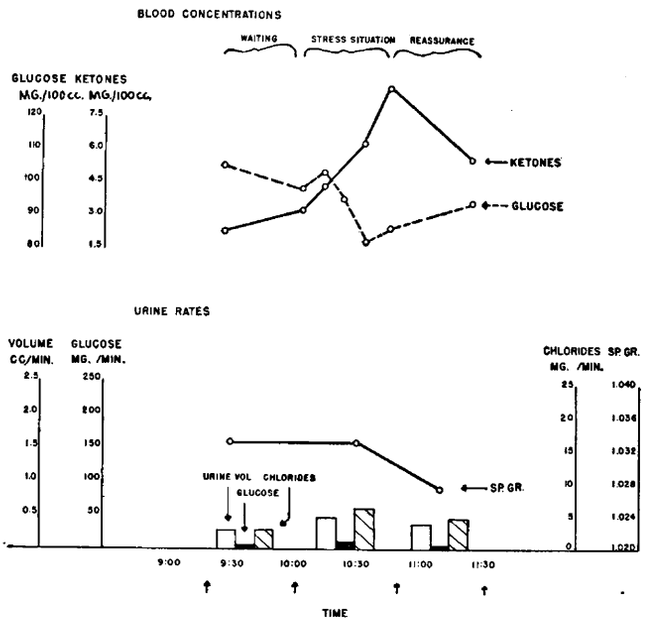

Fig. 3.—Rise in blood ketone concentration occurring in a diabetic woman, 55, taking 15 units of insulin daily, during a period of stress. This change was accompanied by a fall in blood glucose concentration without diuresis.

her conflict with her brother. During the third hour she regained her calm and good spirits when the physician changed his manner and guided the discussion to reassuring and diverting topics. It may be observed that a diuresis developed during the initial period of anxiety and that during the interview period, when the patient also began to feel angry and deprived, her blood ketone concentration rose steeply. Both the diuresis and the ketonemia subsided when the interview turned to more pleasant topics and the patient no longer felt threatened. It should not be inferred from this that the "emotions" were the cause of the metabolic changes but merely that the two types of change—"emotional" and "metabolic"—occurred at the same time as a part of the reaction of

5. Hinkle, Evans, and Wolf.[3a] Hinkle, Evans, and Wolf.[3b] Hinkle, Conger, and Wolf.[4b]

6. Methods of blood glucose determination used in these studies largely exclude reducing substances other than glucose, and yield "normal" values of 50 to 80 mg. per 100 cc.

the subject to the stressful situation.[7] It appears that certain types of emotional reactions often occur at the same time as certain physiological changes—for example, diuresis usually occurred in a setting of anxiety, and an increase in ketonemia usually occurred along with feelings of anger, dejection, and loneliness. Apparently an emotion and a bodily change may accompany each other regularly when both are what might be called "appropriate reactions" to the same stimulus—in this case the stimulus being that aspect of the situation which was interpreted by the subject as threatening.

Diabetic persons show a similar metabolic response to significant psychological stresses, but often it is much greater in magnitude. Figure 3 shows the steady rise in the blood ketones of an unemployed middle-aged seamstress, which occurred when the physician made her angry and dejected by detaining her in the laboratory

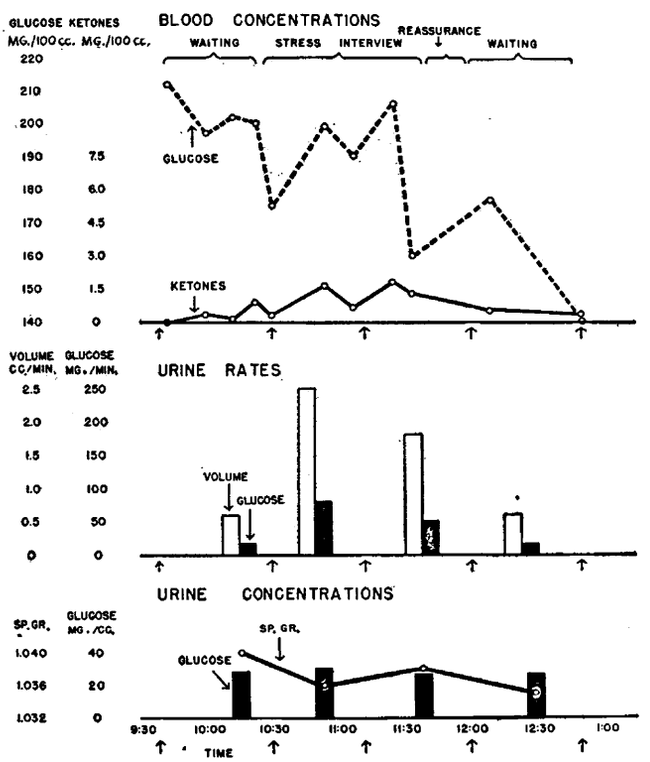

Fig. 4.—Diuresis occurring in a diabetic boy, 15, taking 50 units of insulin daily, who became anxious during a discussion of his conflict with his father. An increase in glucose excretion occurred despite the fall in blood glucose concentration.

at a time when she was expected to report for the first job she had been able to find for several months. The fluctuations of her fasting blood sugar are typical of diabetic persons under stress.

The patient in this study was not anxious, and no diuresis developed, despite the rise in her blood ketones. However, a "stress diuresis" associated with anxiety may be induced in diabetic persons regardless of whether or not they have glycosuria.[7] Figure 4 shows the diuresis which occurred in a boy, 15, during a discussion of his conflict with his father. It may be observed that the rate at which he excreted sugar rose in parallel with the rate at which he excreted water, despite the fact that his blood glucose concentration was falling throughout the entire period. On the other hand, during periods of relative relaxation and security diabetic persons sometimes have

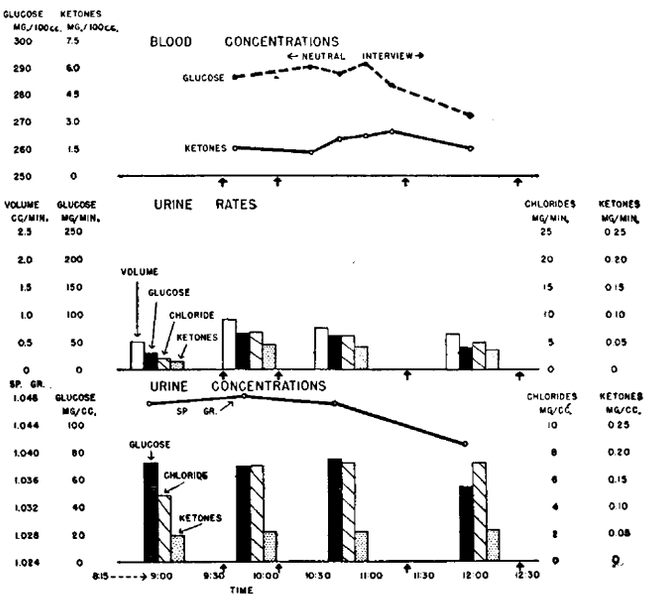

Fig. 5.—Diabetic boy described in Figure 4 exhibiting no polyuria and no symptoms of diabetes during a morning in which he felt relatively secure, relaxed, and diverted, despite the fact that his blood glucose concentration was 286 mg. per 100 cc., and his urine glucose concentration 7%. Blood glucose and ketone concentrations were relatively stable.

a relatively high blood sugar level, and a high concentration of glucose in their urine, without polyuria, thirst, or other symptoms. Figure 5 shows a control study on

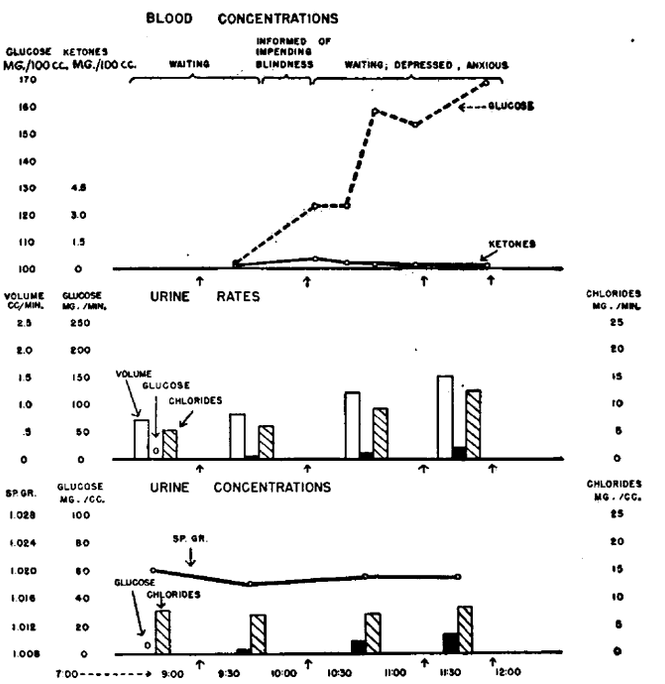

Fig. 6.—Glycosuria and rapid rise in blood glucose concentration in a diabetic man, 30, taking 30 units of insulin daily. He had just learned of his impending blindness.

the same boy, during a morning in which he felt relatively secure, relaxed, and diverted. Despite a blood glucose of 286 mg. per 100 cc. and a 7% glycosuria, he had no polyuria.

7. Hinkle, L. E., Jr.; Edwards, C. J., and Wolf, S.: Studies in Diabetes Mellitus: II. The Occurrence of a Diuresis in Diabetic Persons Exposed to Stressful Life Situations, with Experimental Observations on Its Relation to the Concentration of Glucose in Blood and Urine, J. Clin. Invest. **30**: 818, 1951.

During the experiments illustrated in Figures 3 and 4 the fasting blood sugar level fell, but a rise in fasting blood sugar was observed under certain circumstances of stress. Figure 6 shows the rise in the blood sugar of a man, 30, with retinitis proliferans, which occurred after he learned that nothing could be done to prevent him from losing his vision. It may be observed that glycosuria developed also and that his rate of urine output rose from 0.7 to 1.5 cc. per minute.

The usual initial reaction of a fasting diabetic subject to a conflict situation of importance to him was a transient fall in his blood glucose level accompanied by a rise in ketonemia. If the stress was continued, the blood glucose ceased to fall, and might rise. In labile diabetics in the fasting state, the initial fall in blood sugar during periods of stress was sometimes large enough to precipitate hypoglycemic symptoms. On the other hand, in fasting persons suddenly made very fearful or angry, like the subject of Figure 6, a rapid rise in blood sugar, apparently as a result of epinephrine secretion, often

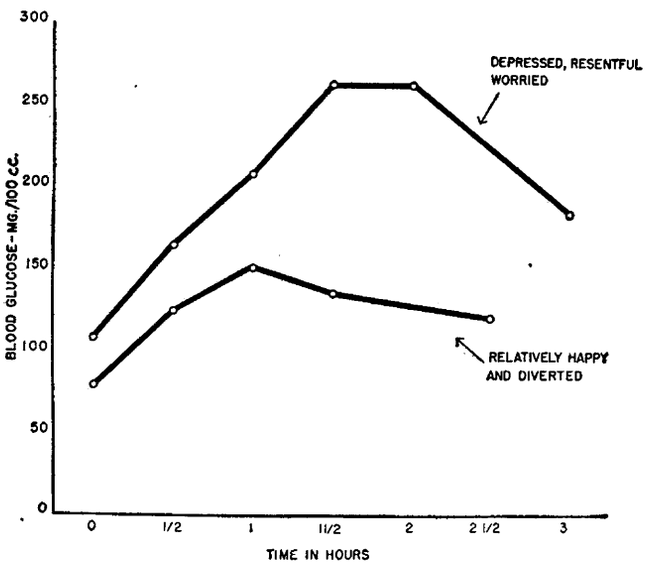

Fig. 7.—Changes in the shape of the oral glucose tolerance curve of a diabetic man, 47, occurring in association with changes in his mood and in his life situation. His diabetes was controlled by diet; he took no insulin.

developed. In addition to these effects on the fasting blood sugar, stress situations also affected the response of the patient to the ingestion of carbohydrate food. Situations associated with loneliness, sadness, and resentment were sometimes associated with a longer and higher ("more diabetic") glucose tolerance curve (Fig. 7); whereas, situations associated with less stress or with anxiety were associated with a flatter and less elevated curve.

When a diabetic person with a relatively high blood glucose level and an established glycosuria is placed in a conflict situation, his reaction to it may include a rapid rise in blood ketones and a greatly increased excretion of water, glucose, ketones, and chlorides (Fig. 8). In short-term experiments such as this we have observed a rise in blood ketones of 19 mg. per 100 cc. in 1½ hours and the excretion of as much as 4.7 cc. of water per minute (282 cc. per hour), 490 mg. of glucose per minute (29.4 gm. per hour), and 25.2 mg. of chloride per minute (1.5 gm. per hour). In a setting of stress a diabetic may excrete enough glucose to deplete his glycogen stores very rapidly (Fig. 9), and at the same time may lose large amounts of chloride and fixed base. Metabolic changes in diabetics in response to stressful

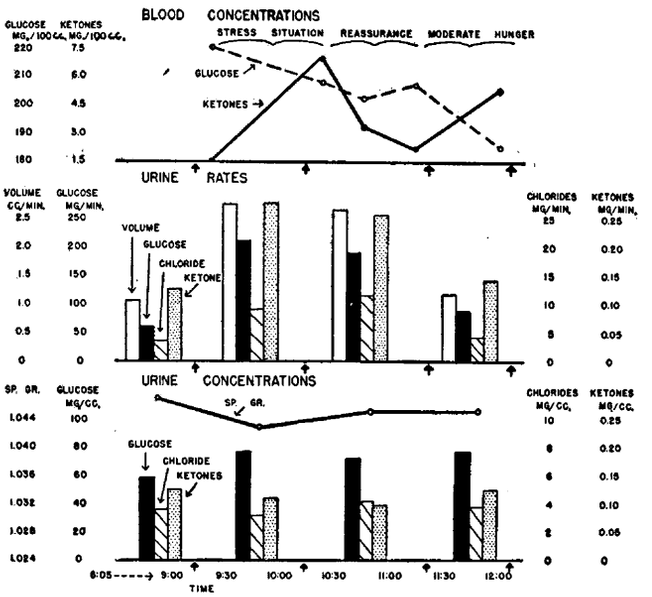

Fig. 8.—Effect of a stress situation on a diabetic subject (taking 90 units of insulin daily) in a borderline state of compensation showing rapid rise in blood ketones, associated with increased excretion of water, glucose, chlorides, and ketones.

life experiences may sometimes be of great magnitude, and they may have serious consequences if not promptly counteracted.

CLINICAL STUDIES

In the group of diabetic persons who were observed at intervals of one or two weeks for three years, it was found that major fluctuations in their symptoms and insulin requirements frequently coincided with important episodes in their lives. Figures 10 and 11 illustrate

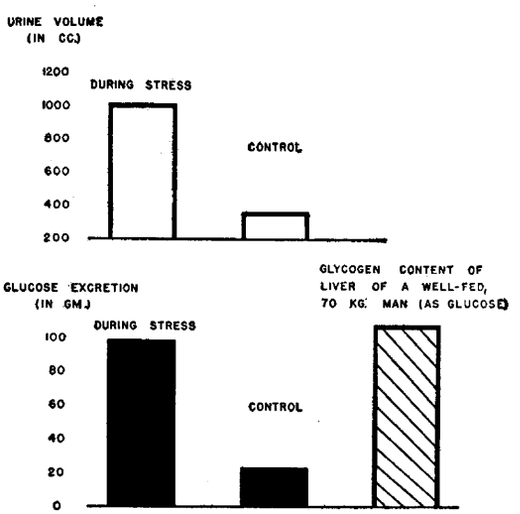

Fig. 9.—Magnitude of glucose and water loss during two comparable four-hour periods in a diabetic girl. Normally available stores of glycogen charted for comparison.

these findings in a girl, 15, who was followed by daily observations on her urine glucose and ketones, and of the events in her personal life.[8] Although she had a constant glycosuria throughout the observation period,

ketonuria, thirst, and polyuria appeared only at times of acute conflicts with her mother. To make certain that these changes were not the result of her willful manipulation of her insulin intake, she was admitted to the hospital for further study. There, under carefully controlled conditions, she was again exposed to a conflict with her mother (Fig. 11). Thirst, polyuria, ketonuria, and dehydration promptly developed and continued for 48 hours. When the differences between the patient and her mother were reconciled, all the manifestations of ketosis disappeared, and the patient was restored to her former state of equilibrium, without use of additional insulin and without changes in fluid intake or diet.

Another patient, a girl, 14, on the hospital ward, was told that on the next morning she would have an operation which she thought was both dangerous and unnecessary. She became extremely anxious and resentful, and during the next 12 hours a ketonemia of 39.8 mg. per 100 cc. developed. Many instances of coma in association with life stress have been observed in persons outside the hospital.[8]

It was found that episodes of ketosis and coma very frequently occurred in a setting of interpersonal stress, although patients often concealed this fact from their physicians. The patients had responded to these conflict situations not only with direct physiological adaptations, but also with changes in their overt behavior which had repercussions on their metabolism. During periods of resentment, rebellion, and hopelessness, they might stop taking their insulin, eat a great deal of food (or stop eating entirely), or expose themselves to illness by such maneuvers as neglecting to sterilize their syringes. Life stress therefore led to ketosis by a variety of mechanisms, although it appeared that the direct metabolic response was the most important of these.

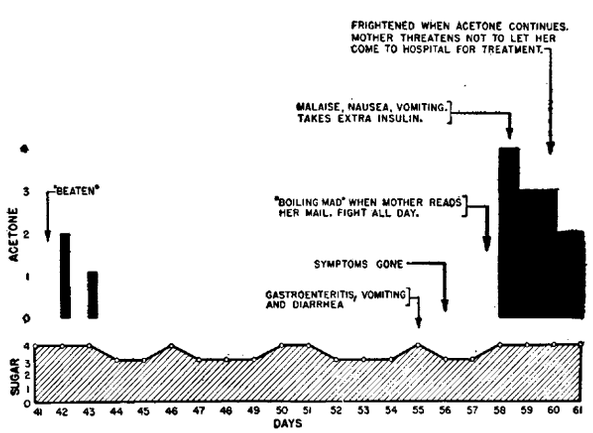

Fig. 10.—Observations on a diabetic girl, 15, showing temporal correlation between episodes of ketonuria and conflicts with her mother. These conflicts appeared to be a more potent cause of ketonuria than the episode of gastroenteritis which occurred on the 55th day.

Similar behavior patterns were observed so frequently in persons with diabetes that it seems unlikely that they could be explained on the basis of chance. For example, a very large percentage of the group had an extraordinary appetite for food years before they had any clinical evidence of diabetes. They were persons who ate more when they felt tense, sad, lonely, or bored, because it made them feel calmer and more contented to do so. Sometimes they found this urge to eat almost uncontrollable. Because of it they had become fat. Because of it they found diabetic diets virtually intolerable. Because of it they "cheated," concealed their eating even

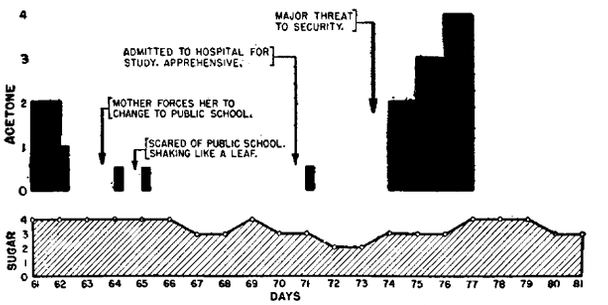

Fig. 11.—Further observations on subject of Figure 10 showing the episode of ketosis which occurred while she was in the hospital and which followed a conflict with her mother (74th day).

from themselves, felt ashamed, and tried to deceive their physician. Because of it adolescent diabetics found solace in the refrigerator or the candy store after an argument with their parents. Such behavior appeared to be almost as characteristic a symptom of diabetes as polyuria. It probably provides an explanation for the apparent paradox of the person who "eats himself into coma." For years physicians have observed that coma develops in patients "after an eating spree." This is such a common clinical phenomenon that the belief that overeating may cause ketosis has remained widespread long after the conclusive demonstration that carbohydrate food always has an antiketogenic effect.[9] Apparently the diabetic person responds to stress with metabolic changes which lead to ketosis, and with an increased intake of food; the coincidence of these two responses has made it appear that the food intake is the cause of the metabolic change.

Other features of these diabetics' behavior and their life experiences which were seen with great regularity may be mentioned briefly. Even adults who had taken insulin for years admitted in confidence their intense dislike for insulin injections. Children and adolescents often detested them, and made the daily injection a painful ordeal for themselves and their parents. A large proportion of the patients had one parent (usually the parent of the same sex) whom they felt to be dominating and restrictive. Toward this parent they exhibited an unusual degree of both dependence and resentment. Periodic outbursts of anger and rebellion directed at this parent had been a feature of their behavior long before their diabetes developed. After the disease began these acute conflicts were accentuated, and were usually accompanied by exacerbations of the illness, including ketosis and coma. This was especially true in the adolescent group. The behavior of a large number of the adolescents was characterized by unreliability, unpredictability, and inability to learn by experience—features typically seen in persons with psychopathic personalities. In diabetics of all ages the onset of the symptoms of the disease usually took place in a setting of stress. Some-

8. Hinkle, L. E., Jr., and Wolf, S.: Experimental Study of Life Situations, Emotions, and the Occurrence of Acidosis in a Juvenile Diabetic, Am. J. M. Sc. **217**: 130, 1949.

9. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, J. Clin. Endocrinol. **1**: 307, 1941.

times this stress was a disease or injury, but more often it was related to the death of a parent, the loss of a husband, or a business reverse, and it was accompanied by feelings of anxiety, dejection, and deprivation. Such feelings often became chronic, and were associated with a feeling of inability to cope with the problems of life. Whether these psychological manifestations must be considered as an integral part of the total disease process which we call "diabetes mellitus" remains to be evaluated, but that they may have a most important effect on our efforts to manage the illness is clear from the available evidence.

COMMENT

Since the fasting blood sugar of labile diabetics may fluctuate rapidly and widely in response to the unpredictable experiences of their daily lives and since the blood sugar level of all diabetics seems to correlate only in the grossest manner with the presence or absence of thirst, polyuria, and ketonuria, it seems evident that random samples of fasting blood sugar provide a less reliable indication of the clinical state of the patient and (except in the detection of insulin reactions) are of less value as a guide to therapy than has been generally thought. For much the same reasons, the presence or absence of glucose in random samples of urine may not give a reliable indication of the clinical state of the patient. On the other hand, since thirst, polyuria, weight loss, and dehydration are direct functions of the volume of urine excreted, the 24-hour urine volume appears to be a relatively reliable indicator of the state of control of the disease. Diabetic persons without impaired kidney function whose urine volume lies between 1 and 2 liters a day maintain their weight and have no symptoms of diabetes. They may or may not have glucose in their urine, depending on the fluctuations in their food intake

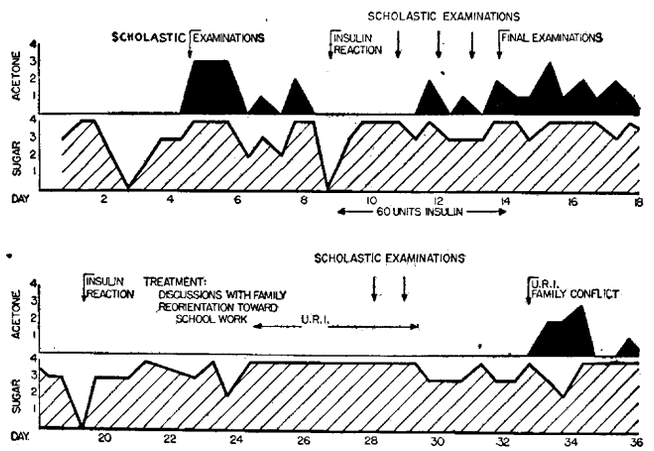

Fig. 12.—Observations on a girl, 15, showing temporal correlation between scholastic examinations (indicated by arrows) and the appearance of ketonuria. Daily dose of insulin was 70 units except when otherwise noted. U.R.I. = upper respiratory tract infection.

and blood sugar level during the day, but usually the number of grams of glucose which they excrete is small. Since ketonemia of moderate degree may occur in the absence of polyuria (Fig. 3) and since the qualitative tests for ketonuria respond to the concentration of ketone bodies in the urine rather than the total amount present, one occasionally sees nondiabetic as well as diabetic persons with a normal urine volume and a positive nitroprusside test. Under these circumstances a "trace of acetone in the urine" does not have the significance which it has when it occurs in association with polyuria.

In similar manner, our therapeutic goals may have to be modified somewhat in the light of added knowledge.

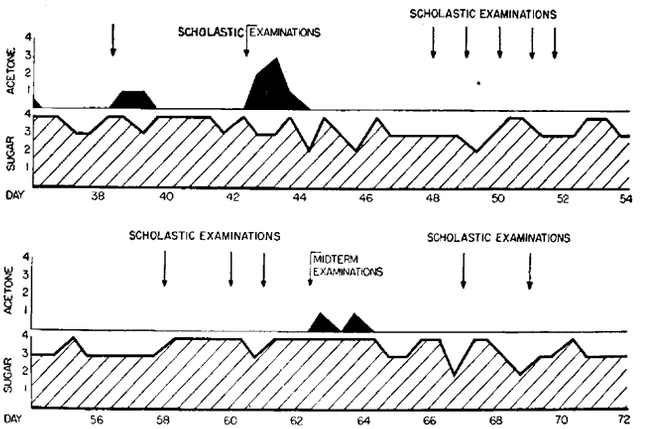

Fig. 13. Further observations on subject of Figure 12 showing the gradual disappearance of episodes of ketonuria when scholastic examinations became less stressful to her.

Ideally, one tries to maintain both the metabolism and behavior of the diabetic person as close to that of the healthy person as possible. It is obvious that treatment limited to the manipulation of diet and insulin cannot attain this goal in many patients, because of their rapidly changing metabolic responses to the events in their daily lives. Furthermore, the craving of many of these persons for food creates an obstacle to precise regulation of their diets. Very few of the persons whom we investigated had even attempted to follow a diet for more than two years, and some of those who tried and thought they were succeeding were found to be making many errors when their daily food intakes were calculated.[3b]

Knowledge that various forms of life stress may have an important effect on the course of diabetes does not necessarily simplify the treatment of the disease, but in some cases it provides one with another tool for dealing with recurrent episodes of ketosis or hypoglycemia. By studying the patient as a person and obtaining a reasonable understanding of his life history and present life situation, the physician can discover without great difficulty those aspects of his private life which are stressful to him. Sometimes, by discussion with the patient, he can so change his attitude toward persons or situations that events which formerly seemed threatening to him cease to seem so. Sometimes the physician can help the patient to modify his life situation by his own actions or by changes in his behavior. Sometimes he can persuade other persons in the patient's environment to alter their attitudes and behavior for the patient's benefit.

An example of the use of this type of therapy is shown in Figures 12 and 13. The patient, a schoolgirl, 15, was referred to the diabetic clinic because of recurrent episodes of ketonuria, which had continued despite all efforts to abolish them by changes in diet or insulin intake. She was the youngest child of an able family, proud of its intellectual attainments. Her father and brother were physicians; her mother was a clubwoman

and civic leader. All three of them expected her to excel in her studies and be a leader in school. They were not sympathetic to adolescent frivolities. The girl, on the other hand, had a mediocre intellect, and longed to take part in the social activities of her friends and schoolmates. In order to meet the demands of her family, she studied for hours each night. She faced the routine daily quizzes of her teachers with great anxiety, mingled with intense resentment because of the burden they placed on her.

The girl had for some time been on a diet carefully prepared by her mother, and each morning 70 units of insulin (25 units of protamine insulin mixed with 45 units of regular insulin) was administered to her by her father. When she was observed carefully, it was found that ketonuria, sometimes associated with thirst and polyuria, occurred whenever she had to face a quiz in school. The physician did not change her insulin intake or diet. During discussions with her parents he pointed out to them that she had neither the ambition nor the ability to be an intellectual leader but that she had the grace and charm to make a successful marriage. They were persuaded to encourage her in social activities and place less emphasis on studies. Meanwhile, the physician encouraged the girl to feel that the friendships and recreation which she wanted were reasonable and healthy desires for a girl her age. As the attitudes of the various members of the family changed, scholastic examinations became less important to her, and the episodes of ketonuria largely disappeared.

Effect of Changing Attitudes, Behavior, and Life Situations of Six Representative Labile Diabetics

Patient	Before Treatment	Under Treatment
Typist, 19, female....	12 admissions in coma or severe ketosis in 4 yr.	No admissions in ketosis in 4 yr.
File clerk, 21, female.	2 admissions in coma, recurrent ketosis and polyuria, insulin requirement 90 to 130 units daily for 10 yr.	Asymptomatic, largely aglycosuric, 60 units insulin daily for 2½ yr.
Student, 21, male....	15 admissions in coma or severe ketosis in 6 yr.	Two 24-hr. admissions in mild ketosis in 2½ yr.
Salesman, 29.....	Daily insulin reactions alternating with ketonuria; recently active tuberculosis; unemployed, depressed, anxious; insulin requirement 180 units daily	No insulin reactions, no ketonuria; tuberculosis arrested; steadily employed, mood much improved for 2 yr.; insulin requirement 160 units daily
Schoolgirl, 15.....	Recurrent ketonuria despite careful control of diet and insulin	Ketonuria largely abolished without change in diet or insulin intake
Spinster, 59.....	Frequent, severe insulin reactions alternating with polyuria and ketonuria; insulin requirement 50 units daily for 10 yr.	Rare, mild insulin reactions, occasional slight polyuria for 2 yr.; insulin intake unchanged

The results which were attained by utilizing such methods in the treatment of six representative patients with labile diabetes from our group are shown in the table. A few of the general principles which were evolved from our experience with the whole group may be outlined briefly. It was found that patients should be seen frequently—at least once a month if they are adolescents or labile adults. After a suitable understanding and rapport is attained between physician and patient, these visits may be brief, but the physician should always maintain an interest in what is happening in his patient's life, and give him an opportunity to discuss his problems and seek advice. He should be encouraged to call on the telephone at any time that unusual symptoms develop, for in this manner many episodes of ketosis may be aborted in their incipiency. The punitive, restrictive, and rejecting attitudes which the patient so often resents in one of his parents should be carefully avoided. Excessive food intake may be regarded as an expected symptom of the disease. It is our practice to present it to patients as undesirable because it leads to obesity and increased glycosuria, but never as a dangerous or stupid breach of faith. We encourage them to discuss the causes and circumstances of their overeating without fear of rejection or disapproval. Likewise, we encourage a free discussion of conflicts with parents or other members of the family, and accompany it with patient attempts to educate the diabetic in the part which his own attitudes and behavior play in causing them. Discussion with parents, husbands, and wives is often helpful, and sometimes judicious advice for changes in employment or living arrangements may be given. However, great caution should be exercised in advising the separation of adolescents from parents with whom they seem to be in constant and bitter conflict. Often this conflict conceals an intense dependency, and hasty intervention may make the patient sicker rather than better. Patience, forbearance, and a willingness to accept any limited improvement that can be attained is sometimes rewarded with gratifying results.

SUMMARY AND CONCLUSIONS

Experimental evidence indicates that stressful life situations may lead to important metabolic changes in persons with diabetes mellitus and that these may be accompanied by emotional changes and changes in behavior. Ketonemia and an increased excretion of water, glucose, and chlorides were observed as well as alterations in fasting blood sugar, which might lead to either hyperglycemia or hypoglycemia.

Study of the life histories and daily experiences of persons with diabetes indicates that many of the apparently spontaneous fluctuations in the syndrome are the results of life stress. The similarities in the life histories of these diabetic persons suggests that developmental, cultural, and psychological factors may have an important influence on the onset and course of the disease. Their behavior under stress, their attitudes toward food, and their feelings toward their parents are often so similar as to suggest that these psychological manifestations might be considered as symptoms of the total disease process.

Treatment directed at alteration of the behavior and attitudes of the patient and his relation to his environment is helpful in abolishing otherwise uncontrollable fluctuations in the course of labile diabetes and in preventing recurrent episodes of ketosis requiring hospitalization. In all cases of diabetes an understanding of the patient and his life situation is necessary in order to understand the course of the disease, the limitations of therapy, and the goal which may be attained.

525 E. 68th St. (Dr. Hinkle).